RE: BURDEN OF MAJOR DEPRESSIVE DISORDER

SUMMARY

- Major depressive disorder (MDD), the most common psychiatric disorder, imposes a considerable economic and humanistic burden (i.e., patient quality of life, impairment of normal activities).

- The total cost of care in the treatment of depression can be impacted by antidepressant length of therapy. Switching, augmentation, and poor adherence with antidepressants can impose a significant burden on the patient and the payor. Effective treatment regimens in which patients are likely to be adherent may contribute to a reduction in this overall economic and humanistic burden.

- Several studies have demonstrated that the costs of medical care vary according to the pattern of antidepressant use. These costs are highest among patients whose therapy is switched/augmented, among patients who discontinue treatment early, and among patients who are non-compliant.

Some information contained in this response may be outside the approved prescribing information for *Wellbutrin XL*. This response is not intended to offer recommendations for administering *Wellbutrin XL* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Wellbutrin XL*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Wellbutrin XL*.

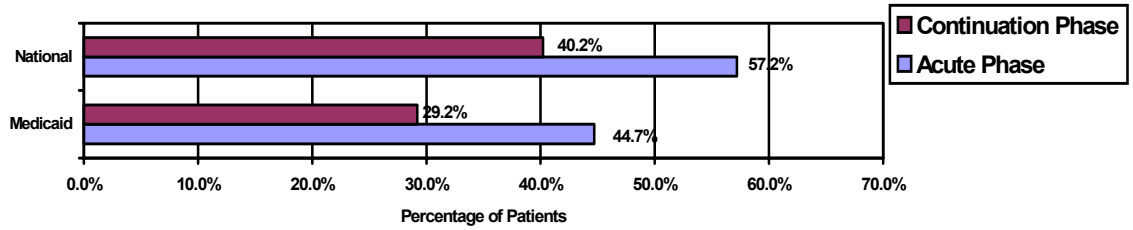
BURDEN OF DEPRESSION

Depression, a serious illness, has become a major public health concern and is responsible for significant social impairment, including deterioration of family and interpersonal relationships, lost work productivity, and general suffering. Major depressive disorder (MDD) is the most common psychiatric disorder in the United States (U.S.) (1). In the U.S., MDD has a lifetime prevalence of 16.2% and a 12-month prevalence of about 6.6% (2). This prevalence corresponds to a national population projection of 32.6 to 35.1 million U.S. adults with lifetime MDD and 13.1 to 14.2 million U.S. adults with a 12-month prevalence of MDD (2).

Despite being a highly treatable disorder that can be managed with a variety of antidepressants from several classes, depression remains largely underdiagnosed, misdiagnosed, and undertreated (3). And despite treatment guidelines for MDD, patients are frequently not receiving adequate doses and duration of antidepressant therapy. According to the American Psychiatric Association (APA) Guidelines for the treatment of Major Depressive Disorder (2000), generally all antidepressants have demonstrated comparable efficacy, thus the choice of antidepressant should be based on factors such as side effects, safety and tolerability, quantity and quality of clinical trial data and cost (4). The APA treatment guidelines consist of an acute phase, during which remission is induced; a continuation phase, during which remission is preserved; and a maintenance phase, during which the patient is protected against recurrence. In many patients, more prolonged therapy is warranted due to the high prevalence of relapse or recurrence of MDD (5). In a recent pooled analysis of 31 randomized trials (N = 4410), the risk of relapse was reduced by approximately 50% when antidepressant treatment was continued for 6 to 36 months following initial treatment response (6). Of the 31 trials, 6 trials were of 2 to 3 years in duration. In these 6 trials, the risk of relapse during the first 12 months was 60% but decreased to 29% during the subsequent 12 to 36 months.

The National Committee for Quality Assurance (NCQA) Health Plan Employer Data and Information Set (HEDIS®) is a performance tool used by more than 90% of America's health plans to measure the percentage of eligible plan members that receive appropriate health care services. The HEDIS antidepressant medication management guidelines are based on APA and the Agency for Health Care Policy and Research (AHCPR) guidelines (4, 7, 8). HEDIS quality accreditation standards for antidepressant medication management recommend that patients be on antidepressant therapy for 90 days for the acute phase treatment of depression. For effective continuation phase treatment, HEDIS also recommends patients be on an antidepressant therapy for at least 180 days. Figure 1 represents the percentage of patients that adhere to the HEDIS guidelines for acute and continuation phase antidepressant medication management on the national and Medicaid levels in 2001 (9, 10).

Figure 1: 2001 HEDIS® Compass Antidepressant Length of Therapy Results



A chart review, in depressed HMO patients (N = 249), evaluated reasons for failure of the HEDIS criteria (11). It was determined in this population that the most common reason for failure to meet the adequate duration of treatment criterion was patient nonadherence with their medication. Twenty-five percent (25%) of the patients reported to their physician that they were adherent, although pharmacy claims showed otherwise.

A retrospective analysis of retail pharmacy prescription claims data from the Dendrite ScriptMax database assessed the medication possession ratio, an indirect measure of adherence, for Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets 150 mg twice daily, Wellbutrin XL® (bupropion HCl extended-release tablets) 300 mg once a day and other antidepressants (12). According to the modified medication possession ratio findings of this retrospective analysis, 37% of patients initiated on *Wellbutrin XL* 300 mg/day were adherent to HEDIS defined acute phase treatment versus 22% of patients initiated on *Wellbutrin SR* 150 mg administered twice daily. Medication possession ratio rates for SSRIs (citalopram, escitalopram, fluoxetine, fluoxetine weekly capsule, fluvoxamine, paroxetine, paroxetine controlled release and sertraline) and SNRIs (nefazodone, venlafaxine and venlafaxine extended-release) were similar to *Wellbutrin XL*. Due to the lack of a diagnosis variable in the Dendrite ScriptMax database, patient inclusion differed from the HEDIS specification. Therefore, the acute phase treatment rates from the Dendrite analysis should not be compared with the HEDIS rates as reported in Figure 1. The difference in adherence between *Wellbutrin XL* and *Wellbutrin SR* may be explained further by the results from the following survey of patients taking *Wellbutrin SR*.

To understand patient adherence, patient satisfaction, and explore patient preference for a once-daily bupropion formulation, a survey was conducted in patients prescribed *Wellbutrin SR* for MDD (13). Results of the survey indicated that 36.8% of patients prescribed *Wellbutrin SR* twice daily do not take their medication as instructed by their physician. Over 26% of the patients missed a dose within the last 24 hours of the survey. Over 54% of those surveyed were 'very interested' in once daily dosing. Reasons

given for interest in a once daily formulation were no second pill to remember/fewer missed doses (61.9%), easier/more convenient (15%) and easier to remember (6.2%).

ECONOMIC BURDEN OF DEPRESSION

In 2000, the total costs associated with MDD were estimated to be $83.1 billion (14). Indirect costs (lost productivity and absenteeism) accounted for 62% of the total, mortality and direct treatment costs accounted for 7% and 31% of the total cost, respectively. Indirect costs have been reported to drive the overall cost of depression. According to Greenberg et al, treatment costs amount to 31% of the total costs associated with depression and drug costs comprise 40% of the treatment costs. Approximately, $26.1 billion was estimated for direct costs for the treatment of depression, $5.4 billion for mortality costs and $51.5 billion for productivity losses from absenteeism and reduced productivity at work. Treatment of depression has been shown to reduce costs, healthcare utilization, and improve productivity in the workplace (15, 16). The relatively low share of drug costs in the overall drug treatment costs was confirmed by Kind and Sorenson, who estimate drug costs to be 11.3% of the direct costs (17).

In a recent study, 1097 employed individuals, identified through the American Productivity Audit, participated in the supplemental Depressive Disorders study to assess lost productivity attributable to depression (18). In this population, depressed workers reported a mean loss of productivity of 5.6 hours/week compared with 1.5 hours/week for non-depressed workers. This lost productivity could cost U.S. employers up to $44 billion per year for depressed patients compared with $13 billion for non-depressed workers.

Studies have also shown increased healthcare costs for depressed patients. In a retrospective assessment of a national managed care plan, 23,712 members with newly diagnosed depression were compared with 23,711 age and gender matched controls (19). In the first year following diagnosis, patients with depression utilized a greater percentage of resources (hospitalizations, ER visits, physician office visits and number of prescriptions) than the matched control group. Total annual healthcare costs in the year following diagnosis were significantly higher for patients with depression ($4067) compared with the matched controls ($1472) ($P < 0.0001$).

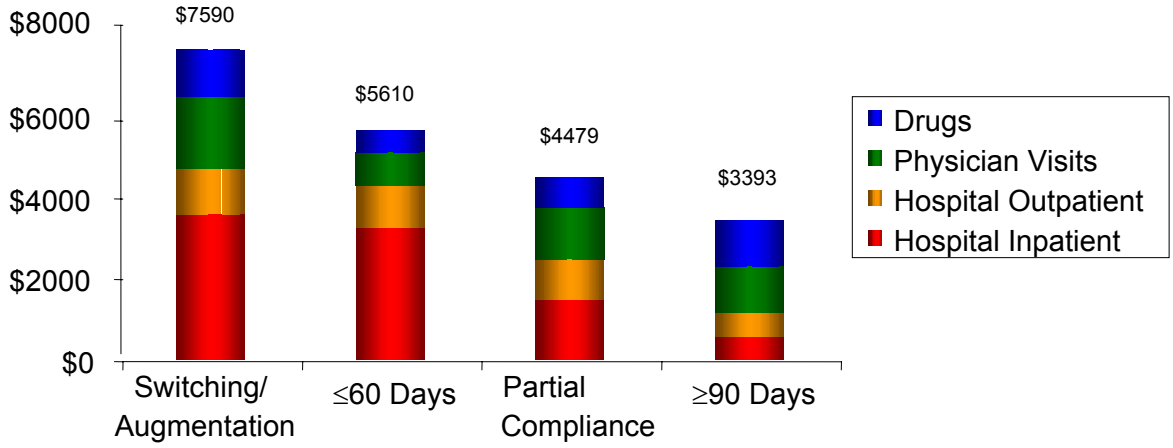
Economic Implications of Medication Adherence

In consideration of the poor performance rates for depression quality measures nationwide, several studies have been conducted to evaluate the economic impact of antidepressant length of therapy.

Thompson and colleagues examined the economic implications of differences in patterns of antidepressant use, such as early discontinuation (≤60 days of therapy), therapy switching/augmenting, partial compliance and continuous use (≥90 days of therapy) (20). Data for this study were obtained from January 1991 to June 1993 from the computerized claims processing system of a large, private, health insurer; a total of 1200 patients were identified.

The authors found that the cost of antidepressant therapy differed significantly by the pattern of drug use during the 12-month follow-up period (Figure 2). The authors concluded that the costs of medical care vary according to the pattern of antidepressant use and these costs are highest among patients whose therapy is switched/augmented or who discontinue treatment early. Early discontinuation (≤60 days of therapy) resulted in an increased cost of more than $2200 per patient annually compared with patients staying on therapy for ≥90 days and switching or augmenting therapy was associated an increased cost of $4197 compared with continuous therapy ≥90 days. Partial compliance resulted in an increased cost of $1086 per patient annually compared with patients on therapy ≥90 days.

Figure 2: Overall Costs of Medical Care over 12 months (20)



Krishnan et al conducted a retrospective assessment of the impact of switching and augmentation on the costs of depression during treatment and 1-year post-treatment (21). Between June 1995 and December 1996, patients diagnosed with MDD (N=2655), prescribed an SSRI within 30 days of diagnosis and enrolled in a national managed care plan who were continuously eligible 6 months before and 1 year after the index depression visit were analyzed. Approximately, 1 of every 5 patients required a second antidepressant (either augmentation or switch) during the treatment period. The cost per month during the treatment period for switchers, augmenters and patients who did not change their index antidepressant (i.e. completers) was $531, $592 and $421, respectively ($P < 0.0001$). The adjusted mean 1-year post-treatment costs were $3415, $4938 and $2728 for switchers, augmenters, and completers, respectively ($P < 0.0001$). The authors concluded that switching and augmentation of antidepressants imposes a significant burden to payors and patients.

Eaddy et al examined the economic implications of differences in patterns of antidepressant use, including early discontinuation (<90 days of therapy), continuous use (≥ 90days of therapy), partial compliance, dose titration and therapy change (22). Data were obtained from a large managed care organization database representing 40 million individuals from 53 health plans. A total of 65,753 patients were identified based on the presence of SSRI therapy between January 2001 and June 2002 and followed for 12 months after initiating SSRI therapy. The authors found that the cost of antidepressant therapy differed significantly by the pattern of drug use during the 12-month follow-up period (Table 1). The authors concluded that the costs of medical care vary according to the pattern of antidepressant use and these costs are highest among patients who discontinue treatment early ($6,289) or have a change in therapy ($7,858). Patients who remained on therapy for at least 90 days had the lowest overall medical costs ($5,143).

Table 1: Annual Overall Medical Costs (22)

	< 90 Days	≥ 90 Days	Partial Compliance	Dose Titration	Therapy Change
% Patients	36%	16%	13%	12%	23%
Inpatient	$2,094	$1,446	$2,040	$1,996	$2,386
Outpatient	$1,427	$1,302	$1,319	$1,499	$1,868
Emergency Department	$309	$159	$177	$238	$302
Physician	$1,434	$1,290	$1,334	$1,584	$2,007
Other	$1,025	$947	$1,038	$1,058	$1,296
	$6,289*	**$5,143**	**$5,909†**	**$6,375***	**$7,858***

* $P < 0.0001$ versus > 90 days cohort
† $P < 0.05$ versus > 90 days cohort

HUMANISTIC BURDEN OF DEPRESSION

Depression imposes a considerable burden on individuals and on society in terms of work productivity, impairment of daily activities, and cost to health care service providers. The World Health Organization (WHO) Global Burden of Disease Survey found that major depression was the leading cause of disability (measured in years lived with a disability) worldwide (23). According to the WHO, mental disorders today constitute 10.5% of the global burden of disease and are projected to increase their share to almost 15% in 2020. By the year 2020, major depression will be second only to ischemic heart disease in the amount of disability experienced by sufferers. This high level of burden is a result of high prevalence and chronicity, early age of onset and high impact on sufferer's lives. The European division of the WHO has launched several mental illnesses programs in Europe to combat the burden of illness imposed by the disease (24).

Depression is associated with greater social and physical impairment, poorer quality of life, more days in bed, fewer pain-free days, higher treatment costs and lower perception of health status than diabetes, hypertension, coronary artery disease, angina, arthritis, back-, lung- or gastrointestinal problems (25). A study of patient-rated utility of prevalent medical conditions found that patients rated the quality and utility of life worse in depression (0.30) than in medical conditions such as chronic renal disease (0.63), severe angina (0.87) and AIDS related dementia (0.52) (26).

Quality of Life Measures

The health-related quality of life (HRQoL) and productivity of 816 patients receiving *Wellbutrin SR* 300 mg/day was evaluated during the 8-week open label phase of a long-term relapse prevention study comparing *Wellbutrin SR* and placebo (27). The Quality of Life in Depression Scale (QLDS) assessed quality of life at baseline and week 8. Productivity was determined using information collected via interview that included missed work hours due to depression, time spent being effective at work, frequency of reduced effectiveness due to depression (0 = never, 1 = rarely, 2 = sometimes, 3 = usually, 4 = always), and hours of overall productivity. Overall productivity was calculated from the sum of productivity lost from work absenteeism and reduced work effectiveness. Only patients who reported working full- or part-time were included in the productivity analysis (466 of 816 patients). The mean QLDS scores improved with *Wellbutrin SR* (18.98 to 10.36, $P < 0.001$). During the last week of treatment, patients lost 1.58 fewer hours from work, were 14.6% more effective on the job, had a decrease of 1.17 points in the scale of reduced work effectiveness, and had 6.37 fewer hours of overall lost productivity as compared with pretreatment values *(*$P < 0.001$ for each variable). Patients that reported a CGI-I score of 1: "very much improved" or 2: "much improved" (responders) to *Wellbutrin SR* during weeks 6 to 8 had greater improvements in both Quality of Life (QOL) and productivity than did

nonresponders *(P* < 0.001). Both responders and nonresponders had similar baseline QLDS and productivity scores.

Quality of life in elderly patients was assessed as a secondary outcome measure during a 6-week, controlled, double-blind, multicenter trial in elderly depressed outpatients randomized to either *Wellbutrin SR* 100 to 300 mg/day (N = 48) or Paxil® (paroxetine HCl) 10 to 40 mg/day (N = 52) (28). All patients were ≥ 60 years old and had a diagnosis of moderate to severe depression. Analysis of this data was performed by Doraiswamy et al, who used the Short Form-36 Health Survey (SF-36) and Quality-of-Life in Depression Scale (QLDS) as the QOL assessment tools (29). Statistical significance was defined as $P < 0.01$ due to concerns about multiplicity in the analysis. The SF-36 is composed of eight individual dimensions that can be further summarized into Mental and Physical component scores. The QLDS contains 34 items that are self-rated, with numerically higher scores correlating to worse QOL. Both the SF-36 and the QLDS were administered at baseline and Day 42 (or time of participant discontinuation). Subjects were divided into three groups based on their HAM-D_{21} scores. Remitters (defined as subjects with a HAM-$D_{21} \leq 7$ at the last visit), partial responders (defined as subjects whose HAM-D_{21} scores decreased by at least 50% between baseline and last visit), and nonresponders.

Wellbutrin SR and *Paxil* demonstrated comparable improvement in QOL measures at Day 42. A pooled analysis of the entire study sample showed significant improvement in the QLDS and the SF-36 Mental Health Index ($P < 0.0001$) at endpoint. Changes in Physical Functioning were not significant ($P < 0.016$). HAM-D_{21} score improvement was correlated with improvement in QLDS ($P < 0.0004$) and SF-36 Mental Component score ($P < 0.0001$), but not the SF-36 Physical Component score ($P < 0.014$). Remitters showed greater improvement than nonremitters on the QLDS and five SF-36 items and also showed greater improvement than partial responders on the QLDS and four SF-36 items. Lower baseline SF-36 Physical and Social Functioning scores showed a trend towards predicting decreased clinical response to treatment. Optimal QOL improvement is associated with remission, although some QOL improvement will occur in partial responders and nonresponders.

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Enclosure: Prescribing Information for *Wellbutrin XL*